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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/833,745	04/13/2001	Joseph Roberts	78728/106	2894

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EXAMINER
PATTERSON, CHARLES L JR

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/05/2002 11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/833,745	ROBERTS ET AL.	
	Examiner	Art Unit	
	Charles L. Patterson, Jr.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/18/01, 8/9/01, 5/10/02 and 8/29/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *7-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 April 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Applicant's election with traverse of claims 7-20 in Paper No. 10 is acknowledged. The traversal is on the ground(s) that Groups I-V all encompass SEQ ID NO:1, with the other groups claiming expanded regions, Group VI also comprises SEQ ID NO:1 and highlights variations and further that there must be a serious burden upon the examiner. Applicants also argue that "the product as claimed can be used in a materially different process" and "[i]t is the enzymatic activity of the polypeptide [of Groups I-VI] that makes it an effective therapeutic…[and] the therapeutic capability…cannot be divorced from the enzyme's activity". They further argue that "separate status of the art may be shown by citing patents" and that Groups V-VI fall within one class (435) and subclass (232)…[and that] Groups VII and VIII also fall within the same class (435)". This is not found persuasive because Group VI apparently is a structurally different product from Groups I-V; even though the enzymatic activity is what is the therapeutic use, the enzyme could be used for other purposes such as its enzymatic activity not related to treatment; though some of the groups are classified in the same class, they are not classified in the same subclass. In this regard it is noted that there is a typographical error in the classification of Group VII, which should be class 424, subclass 94.1.

The requirement is still deemed proper and is therefore made FINAL. However, the examiner will examine Groups I-VI, claims 1-6.

Claims 7-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

The disclosure is objected to because of the following informalities:

In addition to the objection to the drawings shown on the enclosed PTO-948, the examiner objects to Figures 5 and 6. The numbers shown at the top of the figures do not line up with the lanes on the gel.

In the amendment filed 7/15/01, it is requested that paragraph 00127 be substituted. Apparently the correct paragraph is 00128. The examiner has made an attempt to change the entry of the instant amendment but the red ink used was permanent. The simplest way to remedy this is to delete what was in the previous amendment and substitute paragraphs 00127 and 00128.

In the amendment filed 7/18/01 changing the description of Figure 14, the sequences are disclosed as "43-64, respectively". This is 22 sequences and there are only 21 sequences in the figure.

In the same amendment Table 1 is indicated as including SEQ ID NO:1-27, while there are only 19 sequences in the figure. Also, "coordinates" in Table 1 apparently is meant to refer to the residue positions. This is not understood as e.g. SEQ ID NO:1 has 37 residues (amino acids) but the "coordinates" for the first sequence in Table 1 are 838-867. Also, SEQ ID NO:1-6 and 8-11 are amino acid sequences, not nucleotide sequences as shown in Table 1.

In paragraph 133 it is stated that the data from the sequence analysis of the 55 kDa protein is shown in Figure 2. Figure 2 only shows 3 short sequences, so it does not show the data from the sequencing.

In paragraph 146, line 4, it is stated that "below is a graph". No graph is seen below.

Appropriate correction is required.

Claims 1 and 4-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in the recitation of "substantially" on line 2. It is not clear from this recitation how much inhibition of activity in the presence of a histidine analog is envisioned.

Claims 4 and 5 are confusing and apparently incorrect in the recitation of "30,000 to 70,000 daltons" and "56,000 daltons", respectively. According to the second sentence in paragraph 132, the 511 amino acid sequence of SEQ ID NO:10 is "approximately 55 kDa", not SEQ ID NO:1-6 as in the instant claims.

Claim 6 is indefinite in the recitation of "PEGylating" and "PEG". Abbreviations should be avoided in patent applications. A recitation of "polyethylene glycol (PEG)" would overcome this rejection.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-6 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The instant claims are directed to a polypeptide with histidine ammonia lyase activity that is not substantially decreased by a histidine analog. Specifically SEQ ID NO:1-6 are claimed. The specification teaches in paragraph 132 that the gene for the enzyme isolated is SEQ ID NO:12 and the corresponding protein is SEQ ID NO:10. None of SEQ ID NO:1-6 correspond to SEQ ID NO:10 and it is maintained that only SEQ ID NO:10 is taught to have enzyme

activity by the specification. SEQ ID NO:1-4 are shorter than SEQ ID NO:10, while SEQ ID NO:5 is slightly longer. SEQ ID NO:6 contains many Xaa residues, which can be any amino acid. None of SEQ ID NO:1-6 are taught by the specification to have enzymatic activity and it is maintained that without enzymatic activity they have no utility. As to SEQ ID NO:5 and 6 which are close to the length of SEQ ID NO:10, changing even one amino acid residue can effect the activity of an enzyme in an unpredictable way, and absent some showing that the protein having these sequences have activity it is maintained that they do not.

Claims 1-6 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a combination written description and enablement rejection.

The specification teaches in paragraph 132 that the gene for the histidine ammonia lyase from the family *Corynebacteriaceae* was isolated and sequenced and that it was SEQ ID NO:12 and that the corresponding protein was SEQ ID NO:10. The claims are drawn to a polypeptide that has the enzyme ac-

tivity but "is not substantially decreased in the presence of a histidine analog". To start with the only histidine analog shown in the specification is histidinol and it is maintained that the claims should be so limited. It is not at all clear from the specification which protein the effects of histidinol shown in Figures 9 and 10 are for. Is it SEQ ID NO:10 or one of the other sequences? It is not clear from the specification whether something was done to SEQ ID NO:10 to make it resistant to histidinol or whether this resistance is inherently present in SEQ ID NO:10. It is maintained that the specification does not clearly teach one of ordinary skill in the art how to make the enzyme of the instant claims as it is unclear exactly what protein "is not substantially decreased in the presence of a histidine analog". Also, it would not be clear to such a person of ordinary skill reading the instant specification that at the time the application was filed applicants had possession of the claimed invention for the same reasons.

In paragraphs 132 and 133 it is taught that the enzyme has a molecular weight of 55 kDa. Apparently nowhere does the specification teach an enzyme of about 56 kDa, as in claim 5. Also, claims 4 and 5 depend from claim 3, which has sequence of a wide variation in length and therefore molecular weight. Apparently all of these sequences cannot have a molecular weight between 30 and 70 kDa or 56 kDa, and apparently none of the sequences in claim 3 have been shown to have these molecular weights, even SEQ ID NO:5 and 6, absent a convincing showing to the contrary.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by either of Brand, et al. (B2) or Roberts, et al. (A1). Brand teaches a histidine ammonia lyase that is "inhibited competitively by L-histidine hydroxyamate...and to a lesser extent by L-histidinol, D-histidine, and glycine". It is maintained that because of the indefiniteness of "substantially decreased" in claim 1 (see 35 USC § 112 second paragraph rejection, *supra*), the instant reference reads on the instant claims. The molecular weight of 220 kDa in the instant reference was obtained by polyacrylamide gel without SDS and thus cannot be compared with that of claims 4 and 5, which were obtained from SDS gels. Roberts, et al. teaches the isolation and purification of a histidase (histidine ammonia lyase) from *Corynebacteriaceae* that is apparently the enzyme of the instant claims. As discussed *supra*, it is not clear from the specification if something was done to SEQ ID NO:10 to obtain the resistance to histidinol, but absent a convincing showing to the contrary it is maintained that nothing was done. Claim 3 includes SEQ ID NO:6 that has many Xaa's and absent convincing proof to the contrary it is maintained that at least SEQ ID NO:6 reads on the protein taught by the instant references. Sequencing an enzyme and determining its characteristics does not lend anything patentable to the enzyme, *per se*. It is maintained that all of the

characteristics of the instant claims are inherent in the enzyme taught by the instant reference, absent very convincing proof to the contrary.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over either of Brand, et al. (B2) or Roberts, et al (A1) in view of either of Shittigar (A) or Kinstler, et al. (B). As stated *supra*, Brand, et al. and Roberts, et al. teach the enzyme of the instant claim. Shittigar teaches in the paragraph spanning columns 2-3 that polyethylene glycol increases the biological half life and reduces the immunogenicity of an enzyme. Kinstler, et al. teach in column 1, lines 34-55 that polyethylene glycol protects enzymes from proteolysis. It would have been obvious to one of ordinary skill in the art to use polyethylene glycol (PEGylation) on the enzyme taught by Roberts, et al. The motivation would have been to protect against proteolysis, increase half life and/or reduce the immunogenicity.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charles L. Patterson, Jr., PhD, whose telephone number is 703-308-1834. The examiner can normally be reached on Monday - Friday, 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Charles L. Patterson, Jr.
Primary Examiner
Art Unit 1652

Patterson
November 4, 2002